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MAJOR ARTICLE

Routine Infectious Disease Consultation Prior to an Allogeneic Hematopoietic Cell Transplant

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Background. A transplant infectious disease (TID) assessment is essential to select recipients for an allogeneic hematopoietic cell transplant (HCT) and tailor prophylactic and empirical treatment recommendations.

Methods. We performed a retrospective single-center study to describe our model of care based on a routine TID consultation prior to an allogeneic HCT between 2018 and 2022 in 292 adult (≥18-year-old) consecutive patients. We describe the performance of a TID consultation, arbitrarily defined as major (HCT postponement, procedure, cytomegalovirus [CMV] recipient serology reinterpretation) and minor interventions.

Results. Overall, 765 interventions were observed in 257 of 292 (88%) patients: 88 of 765 (11.5%) major and 677 of 765 (88.5%) minor interventions. Among major interventions, HCT was postponed in 8 of 292 (2.7%) patients and a procedure was requested in 18 of 292 (6.2%) patients. The CMV recipient serostatus was changed from indeterminate/low-titer positive to negative in 60 of 292 (20.5%) patients. Among 677 minor interventions, there were 68 (8.8%) additional consultations with other services requested, 260 (33.7%) additional diagnostic tests requested, 102 (13.2%) additional treatments recommended, 60 (7.8%) non-CMV serology reinterpretations performed, 115 (14.9%) deviations from routine anti-infective prophylaxis, and 72 (9.3%) deviations from routine empirical antibiotic treatment recommendations in case of neutropenic fever.

Conclusions. We are proposing a structured, clearly defined, and comprehensive pretransplant checklist for an effective assessment of infectious disease risks and complications prior to an allogeneic HCT. Further studies or experiences like ours could help to define a global strategy or new models of care to be implemented in HCT centers in the future.

Keywords. allogeneic hematopoietic cell transplant; infectious disease consultation; pre-transplant.

Infectious disease complications remain a major cause of morbidity and mortality in allogeneic hematopoietic cell transplant (HCT) recipients, despite recent advances in infectious diseases prevention and treatment and a better understanding of immune reconstitution mechanisms [1, 2]. To further optimize clinical outcomes, a careful and thorough screening of all transplant recipients is required. From the infectious disease point of view, this involves identifying both active and latent infections, as well as past or current exposures to determine an individual's risk and create personalized posttransplant prophylactic and empirical antibiotic strategies. Although a transplant infectious disease (TID) evaluation is performed at many centers prior to an allogeneic HCT, there is a lack of data regarding the content and utility of a pre-HCT TID consultation. The European Society of Clinical Microbiology and Infectious Diseases Study Group of Infection in Compromised Hosts has formulated European recommendations for screening donors and recipients before solid organ transplantation [3]. International consensus recommendations suggest serology screening of the recipient for a number of infectious diseases before HCT; however, there is no universal guidelines in the need and type of a TID consultation prior to an allogeneic HCT [1]. Considering the increasing numbers of allogeneic HCT worldwide and the frequency of infectious disease complications, it becomes urgent to develop uniform screening algorithms to homogenize clinical care and potentially improve clinical outcomes. A TID consultation is routinely performed for all allogeneic HCT recipients at our tertiary care reference center within a month prior to transplantation. This study aims to describe this model of care and interventions prompted by the TID consultation in a large contemporary cohort of allogeneic HCT recipients.

METHODS

Study Design

This is an observational retrospective single-center cohort study of all consecutive adult (≥18-year-old) allogeneic HCT

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recipients from 1 January 2018 to 31 December 2022 who underwent a TID consultation pre-HCT. The study was approved by the local ethics committee. The objective of this study was to describe the frequency of major and minor interventions as a result of a TID consultation.

Definitions

Major interventions were defined as (1) HCT cancellation or postponement, (2) any diagnostic or therapeutic invasive procedure recommended before HCT (eg, bronchoscopy, surgical procedure), and (3) reinterpretation of the recipient cytomegalovirus (CMV) serostatus. Regarding the latter, recipients with a negative CMV serology at the time of their underlying hematologic malignancy diagnosis and an indeterminate or positive with a low immunoglobulin G (IgG) titer (≥0.6 to <50 U/mL) CMV serology and negative pretransplant plasma CMV DNAemia at the time of their TID consultation were considered to have a negative CMV serology, attributed to passive immunity because of blood product transfusions [4]. Hence, they were labeled and considered as CMV recipient negative for their allogeneic HCT [4]. Minor interventions included (1) consultation requests with other specialist services, (2) additional diagnostic test requests, (3) additional treatment recommendations for already existing or newly diagnosed infectious diseases, (4) other-than-CMV recipient serology reinterpretation (eg, *Toxoplasma gondii*, hepatitis A virus [HAV], or hepatitis B virus [HBV] surface antibody indeterminate or low positive IgG titers at the time of TID consultation with negative results at the time of hematologic malignancy diagnosis), (5) changes of standard anti-infective prophylactic recommendations, and (6) changes of standard empirical antibiotic treatment recommendations in case of neutropenic fever post-HCT.

TID Consultation and Institutional Protocols

Historically, a comprehensive list of pertinent clinical and laboratory data collected during a pretransplant TID consultation was created in collaboration between the TID service (C. v. D., D. N.) and the hematology department (Y. C., S. M.-L.), which was finalized in December 2017 and resulted in the current TID pretransplant consultation algorithm described in this manuscript and detailed in Table 1. A TID consultation is routinely performed in all allogeneic HCT candidates in our hospital approximately 4 weeks prior to the transplantation. This TID consultation includes a detailed review of the patient's chart, including prior and current infectious disease complications and diagnostic baseline serological, microbiological, and radiologic workup, as well as an interview with the patient focusing on previous pertinent exposures. Additional diagnostic and treatment recommendations may be made, based on specific exposures, risks, or other problems identified during the TID consultation. According to institutional standard operating procedures, routine anti-infective prophylaxis in all allogeneic HCT recipients includes (val)acyclovir for herpes simplex virus types 1 and 2 and varicella zoster virus, letermovir for CMV (since 2019), co-trimoxazole for *Pneumocystis jirovecii* pneumonia, and fluconazole for antifungal prophylaxis; the latter may be changed to posaconazole in case of invasive mold disease diagnosis prior to HCT or specific environmental exposures. Empirical initial antibiotic treatment for neutropenic fever includes cefepime. Of note, about 60% of patients who undergo an allogeneic HCT at our center come from other centers in the region. In such cases we have access to patient charts and results from their reference center, but the TID pre-HCT consultation is always done in our hospital. The hematology team supervises and assures adherence to the recommendations in the TID consultation.

Data Collection

For this study, patient charts were reviewed in detail for the TID pre-HCT consultation reports, detailing all infectious disease complications during the treatment of hematologic malignancy before HCT; allergies; social history; serology, microbiology, and radiology results; and TID service recommendations. The following data were collected from the institutional HCT database: age, sex, type of hematologic malignancy, CMV donor and recipient serostatus, donor type, conditioning regimen, HCT source, and graft-versus-host disease prevention. Recipient CMV IgG titers (U/mL) were also collected at consultation time and, when available, at the time of malignancy diagnosis.

Statistical Analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Geneva University Hospital [5, 6]. Descriptive statistics were used to characterize the study sample. Median and interquartile range (IQR) were calculated to describe continuous variables and frequencies and percentages for categorical variables. Statistical analysis was performed using Stata version 16 (StataCorp, College Station, Texas).

RESULTS

During the study period, 302 patients underwent an allogeneic HCT in our center. Excluding 6 patients who did not sign a consent form and 4 patients for whom a TID pre-HCT consultation was not performed, there were 292 remaining patients included in this study, 186 (63.7%) men, with a median age of 57 years. The main malignancy diagnosis was acute myeloid leukemia (137 [46.9%]), and a TID pre-HCT consultation occurred at a median of 30 days (IQR, 22–46 days) before transplantation (Table 2).

TID Consultation Results

Results of the complete TID consultation are presented in Table 3. In summary, 217 (74.3%) patients had at least 1 bacterial infection during the treatment of their underlying disease (99/217 [33.9%] had ≥3 bacterial infections), and 38 (13%) patients were diagnosed

Table 1. Routine Checklist for Transplant Infectious Disease Consultation Prior to Allogeneic Hematopoietic Cell Transplant

History-Based Data	Item
Infectious disease history prior to HCT	
Bacterial infections	Pathogen, site, type[a]
Invasive fungal infections	Pathogen, site, diagnostic certainty[b]
Allergies	
Antibiotic agent	β-lactams, sulfa drugs, vancomycin, other
Allergy type and grade[c]	
Allergy-immunology consultation	
Social history	
Origin	Europe vs other
Occupational and other exposures	Outdoor activities/job, gardening, animals, other
Travel history	Africa, Asia, North and South America
Laboratory-based data	
Serology	
Viruses[d]	HIV, HTLV-1/2, HAV, HBV, HCV, HEV, HSV-1/2, VZV, CMV, EBV, HHV-6
Bacteria	Syphilis, tuberculosis[e]
Parasites	Toxoplasmosis, helminthiases[f]
Microbiology	
MDR bacteria screening[g]	MRSA, VRE, ESBL, CPE
Urine culture	
Respiratory virus screening[h]	Influenza A/B, parainfluenza virus 1–4, RSV, hMPV, adenovirus, rhinovirus, coronavirus[h]
Imaging	
Sinus/chest CT	

Abbreviations: CMV, cytomegalovirus; CPE, carbapenemase-producing Enterobacterales; CT, computed tomography; EBV, Epstein-Barr virus; ESBL, extended-spectrum β-lactamase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCT, hematopoietic cell transplant; HCV, hepatitis C virus; HEV, hepatitis E virus; HHV-6, human herpesvirus type 6; HIV, human immunodeficiency virus; hMPV, human metapneumovirus; HSV, herpes simplex virus; HTLV, human T-lymphotropic virus; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; RSV, respiratory syncytial virus; VRE, vancomycin-resistant *Enterococcus*; VZV, varicella zoster virus.

[a]Type of bacterial infection: microbiologically diagnosed infection, clinically diagnosed infection, fever of unknown origin.

[b]Proven, probable, and possible invasive fungal infections according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group definitions.

[c]Allergy type: I (immediate), II, III, IV (delayed). Allergy grade: I (local), II, III (severe systemic reaction: anaphylaxis).

[d]For HIV, HBV, HCV, CMV, and EBV, a plasma quantitative polymerase chain reaction assay (PCR) is also performed at the time of serology. A plasma HEV PCR is also performed in case of HEV-positive serology.

[e]Tuberculosis screening is performed with a blood Quantiferon-TB Gold Plus test.

[f]Helminthiases serology includes the following: trichinellosis, toxocariasis, fasciolosis, filariasis, and strongyloidiasis.

[g]MDR screening includes a nasal, axilla, inguinal, and anal swab.

[h]Routine nasal swab for multiplex respiratory virus PCR screening is performed. Coronavirus screening includes coronavirus OC43, NL63, 229E, HKU1, and severe acute respiratory syndrome coronavirus 2 (the latter since 2020).

with an invasive fungal infection (IFI). Thirty-eight (13%) patients were allergic to an antibiotic agent, but only 9 of 38 (23.7%) had a documented evaluation by the allergy-immunology service prior to our consultation. Overall, 93 (31.8%) patients lived in the countryside and 42 (14.4%) were considered to have important work exposures. Seropositivity for CMV, Epstein-Barr virus, and *Toxoplasma gondii* was documented in 246 of 291 (84.5%), 284 of 291 (97.6%), and 175 of 292 (59.9%) recipients, respectively. Of note, 70 active infections were diagnosed in 65 (22.3%) patients during the TID pre-HCT consultation: 36 bacterial infections (12 acute sinusitis, 10 urinary tract infections, 4 bacteremias, 2 pneumonias, 2 gastrointestinal infections, and 6 other bacterial infections), 32 viral infections, and 2 IFIs, as detailed in Table 3.

TID Consultation Interventions

Only 35 (12%) patients did not have an intervention as a result of their TID pretransplant evaluation. In the remaining 257 (88%) patients, there were 765 interventions documented: 88 of 765 (11.5%) major and 677 of 765 (88.5%) minor interventions (1 patient could have >1 major and/or minor intervention; Table 4).

Major Interventions

First, transplantation was postponed in 8 of 292 (2.7%) patients, due to new lung lesions identified on pre-HCT imaging (n = 4), respiratory tract viral infection (n = 2: respiratory syncytial virus [RSV] and severe acute respiratory syndrome coronavirus 2), and *Pseudomonas aeruginosa* infection (n = 2: lower extremity necrotizing fasciitis and pneumonia). Second, 20 invasive diagnostic procedures were requested in 18 of 292 (6.2%) patients, including a bronchoscopy (n = 13), a biopsy (n = 4: lung in 3 patients, including a thoracentesis and a wedge resection, and muscle in 1 patient), central line removal (n = 2), and a colonoscopy (n = 1). Among

Table 2. Patient Characteristics for 292 Allogeneic Hematopoietic Cell Transplant Recipients

Characteristic	Patients (N = 292)
Demographics	
Age, y, median (IQR)	57 (46.5–66)
Sex, male	186 (63.7)
Underlying disease	
Acute myelogenous leukemia	137 (46.9)
Myelodysplastic syndrome	45 (15.4)
Lymphoma	35 (12)
Acute lymphoblastic leukemia	20 (6.8)
Chronic myeloid/lymphoblastic leukemia	16 (5.5)
Other[a]	46 (15.7)
CMV D/R status	
D^-/R^-	86 (29.4)
D^-/R^+	55 (18.8)
D^+/R^-	26 (8.9)
D^+/R^+	125 (42.8)
HCT-associated variables	
Conditioning regimen	
Myeloablative	69 (23.6)
Reduced intensity	223 (76.4)
Donor	
Matched unrelated donor	130 (44.5)
Matched related donor	61 (20.9)
Haploidentical donor	80 (27.4)
Mismatched unrelated donor	21 (7.2)
HCT source	
Bone marrow	21 (7.2)
Peripheral blood stem cells	271 (92.8)
GvHD prevention[b]	
Cyclosporin A	76 (26)
Mycophenolate mofetil	144 (49.3)
Methotrexate	143 (49)
Tacrolimus	215 (73.6)
Cyclophosphamide	101 (34.6)
Sirolimus	16 (5.5)
Pre-HCT day of infectious disease consultation	
Median, d (IQR)	30 (22–46)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CMV, cytomegalovirus; D^-, donor-negative; D^+, donor-positive; GvHD, graft-versus-host disease; HCT, hematopoietic cell transplant; IQR, interquartile range; R^-, recipient-negative; R^+, recipient-positive.

[a]Other underlying diseases included myeloproliferative syndrome (n = 24), multiple myeloma (n = 12), and hemoglobinopathy (n = 3).

[b]Patients could have received >1 type of immunosuppression.

Table 3. Results From Routine Transplant Infectious Disease Consultation Prior to an Allogeneic Hematopoietic Cell Transplant

Characteristic	Positive/Total, No. (%)
Prior infectious disease	
Bacterial infections	
≥1 bacterial infection	217/292 (74.3)
≥3 bacterial infections	99/292 (33.9)
Neutropenic fever episodes	411
FUO	116/411 (28.2)
MDI	184/411 (44.8)
CDI	109/411 (26.5)
MDR bacteria[a]/total identified pathogens	14/267 (5.2)
Clostridioides difficile infection	21/292 (7.2)
Invasive fungal infections	38/292 (13)
Site, lungs	35/38 (92.1)
Diagnostic certainty, proven	7/38 (18.4)
Pathogen, *Aspergillus* spp	14/38 (36.8)
Allergy[b]	38/292 (13)
β-lactams	21/62 (33.9)
Co-trimoxazole	11/62 (17.7)
Vancomycin	8/62 (12.9)
Allergy grade III (systemic reaction/ anaphylaxis)	5/62 (8)
Allergy-immunology service consultation	9/292 (3)
Social history	
Origin, Europe	185/292 (63.3)
Work-related exposures	42/292 (14.4)
Residence, countryside	93/292 (31.8)
Travel history	
Africa	26/292 (8.9)
US (general)	23/292 (7.9)
US (California, Arizona, Nevada)	6/23 (26)
South America	12/292 (4.1)
Serology	Positive/Tested, No. (%)
HIV	4/292 (1.4)
HTLV-1/2	2/291 (0.7)
HAV	217/291 (74.6)
HBV	
HBsAg	2/291 (0.7)
Anti-HBs	180/291 (61.8)
Anti-HBc	22/291 (7.6)
HCV	0/291
HEV	66/292 (22.6)
HSV-1	222/291 (76.3)
HSV-2	77/291 (26.5)
VZV	287/292 (98.3)
CMV	246/291 (84.5)
EBV	284/291 (97.6)
HHV-6	259/263 (98.5)
Syphilis	1/292 (0.3)
TB (Quantiferon TB Gold Plus test)	12/292 (4.1)
Indeterminate	16/292 (5.5)
Toxoplasmosis	175/292 (59.9)
Helminthiasis	19/292 (6.5)
Microbiology	Positive/Tested, No. (%)
MDR screening	
MRSA	0/292
ESBL	30/292 (10.3)
VRE	1/292 (0.3)

the 13 bronchoscopies, 9 were negative and a pulmonary bacterial infection or IFI was ruled out, whereas in 4 cases an infection was diagnosed and treated: *Pseudomonas aeruginosa* pneumonia (n = 2), *Pneumocystis jirovecii* pneumonia (n = 1), and lung lesions due to *Actinomyces* spp (n = 1). The 4 biopsies revealed the following: pulmonary IFI (n = 2, due to Mucorales in 1 case, due to nonidentified mold in the other case), a cryptogenic pneumonia (n = 1), and *Pseudomonas aeruginosa* myositis and necrotizing fasciitis (n = 1). Third, CMV-R serology was reinterpreted from

Table 3. Continued

Characteristic	Positive/Total, No. (%)
CPE	1/292 (0.3)
Urine culture[c]	18/292 (6.7)
NPS respiratory virus	27/250 (10.8)
SARS-CoV-2 (from 2020)	3/153 (1.9)
Imaging	Abnormal/Performed, No. (%)
Sinus CT	20/288 (6.9)
Chest CT	47/290 (16.2)
Infection diagnosed during pre-HCT consultation	62/292 (21.2)
Bacterial	25/62 (40.3)
Viral[d]	32/62 (51.6)
Fungal[e]	2/62 (3.2)

Data are presented as No. (%).

Abbreviations: Anti-HBc, hepatitits B core antibody; Anti-HBs, hepatitis B surface antibody; CDI, clinically diagnosed infection; CMV, cytomegalovirus; CPE, carbapenemase-producing Enterobacterales; CT, computed tomography; EBV, Epstein-Barr virus; ESBL, extended-spectrum β-lactamase; FUO, fever of unknown origin; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HHV-6, human herpesvirus type 6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T-lymphotropic virus; MDI, microbiologically diagnosed infection; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; NPS, nasopharyngeal swab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TB, tuberculosis; US, United States; VRE, vancomycin-resistant *Enterococcus*; VZV, varicella zoster virus..

[a]MDR bacterial pathogens included 12 ESBL-producing gram-negative bacilli, 1 *Pseudomonas aeruginosa*, and 1 VRE.

[b]Thirty-eight of 292 patients had an allergy history, among whom 62 allergy events were documented. Allergic reaction to β-lactams included penicillins (n = 12), cephalosporins (n = 7), penicillins and cephalosporins (n = 1), and carbapenems (n = 1).

[c]Urine culture: Only monomicrobial cultures for pathogenic bacteria were considered.

[d]Viral infections included 30 respiratory tract viral infections, 1 CMV reactivation, and 1 zoster infection.

[e]Fungal infections included 1 *Pneumocystis jirovecii* pneumonia and 1 possible pulmonary aspergillosis.

indeterminate/low IgG titer positive to negative in 60 of 292 (20.5%) patients with negative CMV serology at the time of hematologic malignancy and an indeterminate (between 0.6 and 3 U/mL; n = 10 [16.7%]) or low positive (between >3 and <50 U/mL; n = 50 [83.3%]) pretransplant CMV IgG titer and negative pretransplant CMV DNAemia. Among them, only 1 patient (1/60 [1.6%]) developed a positive plasma CMV DNAemia during 6-month follow-up posttransplant, attributed to either CMV-positive donor or a new primary CMV infection posttransplant [4].

Minor Interventions

Minor interventions are shown in Table 5. First, overall, 68 additional consultations with other specialist services were requested in 63 (21.6%) patients, including the pulmonary (n = 18), allergy-immunology (n = 18), and ear-nose-throat (n = 10) services. A consultation with the allergy-immunology service was requested in case of an unclear or not well-documented allergy history in the recent or remote past or during prior chemotherapy cycles. Second, a large variety of additional diagnostic tests were requested (n = 260), considering different exposures and risk factors documented during the

Table 4. Major and Minor Interventions Recommended Based on a Pretransplant Infectious Disease Consultation in 292 Allogeneic Hematopoietic Cell Transplant Recipients

Intervention	Patients[a] (N = 292)	Interventions[a] (N = 765)
No intervention	35 (12)	
All interventions[a]	257 (88)	765 (100)
Major[a]	86 (29.4)	88 (11.5)
Postpone transplantation	8 (2.7)	8 (1.1)
Procedure requested[b]	18 (6.2)	20 (2.6)
CMV serology reinterpretation[c]	60 (20.5)	60 (7.8)
Minor[a,d]	191 (65.4)	677 (88.5)
Other service consultation requested	63 (21.6)	68 (9)
Additional test requested	123 (42.1)	260 (34)
Additional treatment recommended	87 (29.8)	102 (13.3)
Serological reinterpretation (other than CMV)	44 (15.1)	60 (7.8)
Deviation from routine prophylaxis recommendations	108 (37)	115 (15)
Deviation from routine neutropenic fever empirical treatment recommendations	67 (23)	72 (9.4)

Data are presented as No. (%).

Abbreviation: CMV, cytomegalovirus.

[a]One patient could have >1 major and/or minor intervention.

[b]Procedures requested included bronchoscopy (n = 13), biopsy (n = 3), colonoscopy (n = 1), lung wedge resection (n = 1), and central line removal (n = 2).

[c]False-positive CMV serology due to posttransfusional passive immunity was suspected if immunoglobulin G anti-CMV titers were low and confirmed with a negative serology at malignancy diagnosis.

[d]A detailed description of all minor interventions is presented in Table 5.

TID consultation interview. Third, an anti-infectious treatment was proposed or reevaluated in 102 cases during TID consultation, predominately antibacterial (n = 43) and antifungal (n = 31). In infections diagnosed prior to the TID consultation and already under treatment, particularly IFI, a careful medical record review was performed to decide on whether the administered treatment should be continued, changed, or adjusted. Fourth, in 22 of 292 (7.5%) patients, indeterminate or low-positive IgG titer *T gondii* serology results were reinterpreted and considered negative, while HAV and HBV serologies were reinterpreted in 11 of 292 (3.8%) and 27 of 292 (9.2%) patients, respectively. Fifth, deviation from the standard antifungal and *Pneumocystis jirovecii* pneumonia prophylaxis recommendations was documented in 104 of 292 (35.6%) and 11 of 292 (3.8%) patients, respectively. Antifungal prophylaxis was modified because of an IFI diagnosis in 31 of 104 (29.8%), potential exposures in 48 of 104 (46.1%), and other reasons in 25 of 104 (24%) patients; the latter included prolonged neutropenia (n = 15), azole-resistant *Candida* or *Trichosporon* colonization (n = 5), suspect imaging (n = 2), hepatotoxicity (n = 2), or unknown reasons (n = 1). Sixth, deviation from the standard neutropenic fever empirical antibiotic treatment recommendations was documented 72 times. Empirical antibacterial treatment in case of neutropenic fever was adjusted based on prior multidrug-resistant (MDR)–pathogen colonization in 35 cases, due to prior allergy to

Table 5. Minor Interventions Recommended as Part of the Pretransplant Infectious Disease Consultation in 292 Allogeneic Hematopoietic Cell Transplant Recipients

Intervention	Minor Interventions (n = 677)
Other service consultation requested	68 (10)
Pulmonary	18 (2.6)
Allergy-immunology	18 (2.6)
Ear, nose, and throat	10 (1.5)
Tropical medicine	8 (1.2)
Other[a]	14 (2.1)
Additional test requested	260 (38.4)
Serology	160 (23.6)
Bacterial[b]	23 (3.4)
Fungal[c]	74 (10.9)
Viral[d]	23 (3.4)
Parasitic[e]	40 (5.9)
Molecular	61 (9)
Bacterial[f]	8 (1.2)
Viral[g]	51 (7.5)
Parasitic[h]	2 (0.3)
Microbiology[i]	11 (1.6)
Imaging	24 (3.5)
Additional sinus CT	4 (0.6)
Additional chest CT	17 (2.5)
Other[j]	3 (0.4)
Other[k]	4 (0.6)
Additional treatment recommended	102 (15.1)
Antibacterial	43 (6.4)
Antifungal	31 (4.6)
Antiviral	9 (1.3)
Antiparasitic	6 (0.9)
Latent tuberculosis	13 (1.9)
Serological reinterpretation (other than CMV)	60 (8.9)
Toxoplasmosis	22 (3.2)
Hepatitis A or B virus	38 (5.6)
Deviation from routine prophylaxis recommendations	115 (17)
Antifungal prophylaxis	104 (15.4)
Posaconazole	73 (10.8)
Isavuconazole	17 (2.5)
Echinochandins	6 (0.9)
Other[l]	8 (1.2)
Pneumocystis jirovecii pneumonia prophylaxis[m]	11 (1.6)
Deviation from routine neutropenic fever empirical treatment recommendations[n]	72 (10.6)
Carbapenem	34 (5)
Piperacillin-tazobactam	14 (2.1)
Daptomycin	5 (0.7)
Vancomycin	2 (0.3)
Other[o]	17 (2.5)

Data are presented as No. (%).

Abbreviation: CMV, cytomegalovirus; CT, computed tomography.

[a]Other included general surgery (n = 3), radiology (n = 2), maxillofacial surgery (n = 2), gastroenterology (n = 1), gynecology (n = 1), vascular surgery (n = 1), cardiology (n = 1), ophthalmology (n = 1), urology (n = 1), and dentistry (n = 1).

[b]Additional bacterial serologies included TB-Spot (n = 11), urinary antigen for *Legionella* spp and *Streptococcus pneumoniae* (n = 3), leptospirosis (n = 2), *Coxiella* spp (n = 2), *Bartonella* spp (n = 2), brucellosis (n = 1), Lyme disease (n = 1), and *Franciscella* spp (n = 1).

[c]Additional fungal serologies included *Histoplasma* spp (n = 32), *Coccidioides* spp (n = 22), β-D-glucan (n = 8), *Cryptococcus* serum antigen (n = 6), other endemic mycosis (n = 4), and galactomannan enzyme immunoassay (n = 2).

[d]Additional viral serologies included additional CMV serology (n = 6), CMV avidity testing (n = 4), additional hepatitis B virus (HBV, n = 7) and hepatitis A virus (n = 2) serology, additional Epstein-Barr virus (n = 2) serology, JC virus (n = 1), and HSV-2 (n = 1).

[e]Additional parasitic serologies included leishmaniasis (n = 12), Chagas disease (n = 9), toxoplasmosis avidity testing (n = 8), additional toxoplasmosis serology (n = 5), additional strongyloidiasis testing using a Baermann test (n = 4), and malaria test (n = 2).

[f]Additional molecular diagnostic tests for bacterial pathogens included *Chlamydia/Mycoplasma* (n = 4), Whipple disease (n = 2), sexually transmitted disease (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*) screening (n = 2).

[g]Additional molecular viral diagnostic tests included additional nasopharyngeal swab (NPSs) for respiratory virus multiplex polymerase chain reaction (PCR) (n = 18), additional plasma CMV PCR (n = 12), plasma hepatitis E virus (HEV) PCR (n = 7), additional plasma HBV PCR (n = 6), stool HEV PCR (n = 2), additional NPS PCR for SARS-CoV-2 (n = 2) and influenza virus (n = 1); human papillomavirus screening (n = 1), plasma human herpesvirus 8 PCR (n = 1), and plasma BK virus PCR (n = 1).

[h]Additional molecular tests for parasitic infections included stool PCR for strongyloidiasis (n = 1) and a follow-up plasma toxoplasmosis PCR (n = 1).

[i]Additional microbiological tests included blood cultures (n = 4), urine cultures (n = 3), stool cultures (n = 2), atypical mycobacterial stool culture (n = 1), and additional inguinal swab (to exclude *Candida glabrata* colonization, n = 1).

[j]Other radiology tests included abdominal CT (n = 2) and positron emission tomography (n = 1).

[k]Other tests included trough antifungal drug serum concentrations (n = 3) and 12-lead electrocardiography (n = 1).

[l]Other antifungal prophylaxis included voriconazole (n = 6) and liposomal amphotericin B (n = 2).

[m]Prophylaxis for *Pneumocystis jirovecii* pneumonia was changed to atovaquone (n = 10) and aerosolized pentamidine (n = 1).

[n]Deviation from routine antibiotic empirical treatment recommendations were prompted by reported antibiotic allergies (n = 11), multidrug bacterial pathogen colonization (n = 35), and other reasons (n = 24): prior infection or suspicion of bacteria resistant to cefepime (n = 10), primary antibiotic prophylaxis recommended (n = 10), asymptomatic bacteriuria (n = 2), recent prior *Clostridioides difficile* infection (n = 2), decolonization recommended because of prior methicillin-susceptible *Staphylococcus aureus* infection (n = 2).

[o]Other included the following: aztreonam + vancomycin (n = 1), aztreonam + daptomycin (n = 1), ceftolozane-tazobactam (n = 1), ceftazidime-avibactam (n = 1), fluroquinolone (n = 6), co-amoxiclav (n = 6), and metronidazole (n = 1).

β-lactams in 11 cases, while a large number of additional reasons prompted further changes (eg, prior *Clostridioides difficile* infection, prior infections with cefepime-resistant pathogens), as detailed in Table 5. Cefepime was replaced by a carbapenem (n = 34), piperacillin-tazobactam (n = 14), glyco/lipopeptide (n = 7), aztreonam with glyco/lipopeptide (n = 2), *Pseudomonas*-acting fluoroquinolone (n = 6), co-amoxiclav (n = 6), ceftolozane-tazobactam (n = 1), or ceftazidime-avibactam (n = 1), and metronidazole was added in 1 case.

Additional Actions

After reviewing the above results, the following screening tests were removed from the TID pretransplant checklist: urine culture, hepatitis E, and human herpesvirus 6 (HHV-6) serology. The latter were considered redundant due to the fact that hepatitis E virus (HEV), as all RNA viruses, does not reactivate in periods of immunosuppression and the prevalence of HHV-6 positive serology is >95% in the adult population [7–9]. In contrast, hepatitis E and HHV-6 polymerase chain reaction (PCR) molecular testing was added to the screening list for viruses, to detect recent

HEV infection prior to transplantation and patients with integrated HHV-6 virus.

DISCUSSION

This single-center cohort study shows that a structured, detailed, prospective infectious disease evaluation prior to transplantation can be an important tool in the management of allogeneic HCT recipients. At least 1 intervention was prompted in 9 of 10 patients because of the TID consultation, having potential direct and indirect effects on clinical outcomes. It is likely that many of those interventions could have been made as a result of the patients' assessment by the treating hematology team either pre- or posttransplant. However, we believe that using a well-defined checklist to consistently assess the risks and challenges associated with infectious disease complications as part of a TID consultation in the pretransplant setting may allow for timely identification and management of potential problems. The key role of the TID consultant may be to identify the problem and coordinate with the hematology team in terms of additional actions needed to be taken, to ultimately assure the safe transition of patients to their transplantation. The findings of this study have allowed us to further validate our model of care and reinforced our decision to maintain a routine pretransplant TID consultation in all allogeneic HCT candidates. It should be noted that close and continuous collaboration between infectious disease and hematology teams in our center has allowed full adherence to TID consultation and close follow-up of the propositions made by our team.

The clinical importance of a pretransplant TID consultation is nicely shown by the number and importance of the major interventions recommended. The identification of active infections with potential dismal clinical outcomes led to postponing an HCT after the successful management of those infections in a small number of patients. For instance, it has been well described that allogeneic HCT recipients with RSV infections may have poor clinical outcomes [10]. In our routine TID consultation we perform a nasopharyngeal swab and we were able to diagnose 30 respiratory viral infections, mostly asymptomatic, but leading to postponing an HCT in 2 cases. In contrast, we were able to show that identification of an IFI prior to an allogeneic HCT did not necessarily prevent patients from being transplanted, as already reported previously [11–13]. In fact, many patients were diagnosed with an IFI prior to their TID evaluation and none of them had to have their HCT postponed or cancelled, based on timely initiation of active and well-tolerated antifungal treatment [14, 15]. Furthermore, with the procedures recommended as part of the TID consultation, we were able to rule out and avoid treatment for a fungal pulmonary infection in 9 patients, whereas a microbiological diagnosis for a lower respiratory tract infection was documented in 7 additional cases, prompting initiation of targeted treatment.

An important intervention, not adequately described until today, was the very thorough review of the CMV serostatus of allogeneic HCT recipients. The recipient CMV serostatus is a piece of essential information in the setting of HCT. In the pre-letermovir era, the recipient CMV serostatus had an impact on donor selection. Nowadays, it is important in defining the population to benefit from primary CMV prophylaxis with letermovir [16]. Considering its implications, it is pertinent to accurately define the recipient CMV serostatus prior to an allogeneic HCT. In that respect, CMV serology is routinely reviewed in our center at the time of the TID consultation and compared (when available) with the CMV serology at the time of the hematologic malignancy diagnosis. We identified 60 patients whose CMV serology was negative at the time of their underlying hematologic malignancy diagnosis and who had an indeterminate or low positive IgG titer at the time of their pretransplant TID consultation [4]. As patients remain mostly hospitalized and at low risk to develop a primary CMV infection between the diagnosis of their hematologic malignancy and their transplant, we considered those serologies as "false-positive," due to passive immunity in the context of immunoglobulin or blood transfusions, and reclassified the CMV recipient status from positive to negative in all those patients, with only 1 of the 60 patients with reclassified CMV serology developing CMV DNAemia posttransplant [4, 17].

Following a TID consultation, prophylactic antifungal recommendations were altered in 1 of 3 patients. Fluconazole is the routine primary antifungal prophylaxis at the time of transplantation in our center. During our routine TID consultation, we collect information on potential high-risk mold exposures, such as living in the countryside or near vineyards, gardening, or other recreational or occupational exposures. In such cases we change our recommendation to posaconazole prophylaxis. Similarly, we observed several proposed changes in routine antibacterial empiric treatment for neutropenic fever in case of patients colonized by extended-spectrum β-lactamase (ESBL)–producing bacteria. Prompt initiation of appropriate empiric treatment of neutropenic fever has a significant impact on mortality [18]. This should be considered during an era with increasing prevalence of MDR bacteria, hence an approach based on pre-HCT screening seems to be highly necessary [18]. In that context, a number of infections were diagnosed during the TID consultation. Although the indication to treat was based on the diagnostic test result and clinical relevance, considering that some patients might have been completely asymptomatic, it is likely that such diagnoses might have led to the administration of unnecessary antibiotic treatment courses. More data are required to assess the utility of additional diagnostic tests in asymptomatic patients pretransplant and such interventions should be further studied in the future, including an antibiotic stewardship scope. Additional antibiotic treatment recommendations were also made due to prior

allergies to different antibiotic compounds identified during a TID consultation. This is pertinent as patients often require prophylactic or therapeutic administration of antibiotic agents, and reported allergies may limit our ability to properly treat them. Only a minority of allergic patients had a documented allergy-immunology consultation and definitive documentation of their allergy prior to our consultation. Considering the importance of β-lactams and co-trimoxazole in the short- and long-term management of allogeneic HCT recipients, it is pertinent to timely identify and document potential allergy issues in the setting.

There are no specific guidelines in terms of performing a baseline sinus or chest computed tomography (CT) prior to an allogeneic HCT. We observed that almost 20% of sinus and/or chest CT scans performed were abnormal at the time of pretransplant evaluation in our patients. Some of those abnormalities could be preexisting, due to prior diagnosed infections. However, a fair number of patients were found to have new lesions on their imaging tests. Whether a routine recommendation for a baseline sinus and/or chest CT should be considered remains to be defined, after carefully weighing the potential benefit of securing an early diagnosis of a potentially serious infection with the cumulative radiation risk and higher costs. However, based on our experience someone could argue that a baseline sinus and/or chest CT not only helps to diagnose new infections, but also to have a reference imaging test as a comparator for the future.

Based on patients' social history, additional diagnostic tests were requested, including serologies for different endemic mycoses or parasitic infections. The large variety of requested tests reflects the myriad of infectious disease exposures and situations present in this patient population. This further highlights the need for a personal approach and customization of a TID consultation prior to transplantation. A routine TID consultation is also the perfect setting for TID specialists to meet with the patient and future HCT recipient, to explain potential risks and infectious disease complications after transplantation, to describe their role in the transplantation process, and to provide counseling about lifestyle changes, traveling, or other activities until full recovery of their immunity. This is an opportunity for counseling on infectious risks, prevention, and vaccination strategies for the patients and their families as well. Finally, during the TID consultation, pertinent information on the types and duration of antimicrobial prophylaxis can be shared with the patients, explaining the utility of prophylaxis, with the detailed role of each molecule and potential secondary effects, which is the best way to improve long-term adherence.

Our study was not designed to prove the effectiveness or cost-efficiency of a TID pre-HCT consultation, nor the impact of our interventions on clinical outcomes. The latter was not feasible due to the study's retrospective observational design, the fact that a TID consultation was performed even before the study period—albeit in a less intensive and organized fashion, not allowing potential comparison with historical controls, and considering the multitude of potential variables influencing outcomes in allogeneic HCT recipients. We acknowledge that the request of numerous screening tests, including CT imaging and additional molecular testing, in asymptomatic patients could increase the financial burden and lead to potential unnecessary transplant postponement or tests, with further increases in the overall cost of care. However, considering the time lag between pretransplant evaluation and transplantation, none of the recommended additional investigations by the TID consultation resulted in any delays of transplantation. Nevertheless, the cost-effectiveness of a TID pretransplant consultation should be further examined in future studies, in order for the best algorithm model to be defined. The checklist proposed may not necessarily be an "all inclusive" list, and further additions or deletions may be required based on different settings. Regular reviews have allowed us to reassess the utility or redundancy of the requested screening tests, with elimination (eg, HEV serology, urine culture) or addition (eg, HEV PCR testing) of different tests over time. It is likely that the same list may not apply to all centers or countries and may require further adjustments to reflect the epidemiology and practices of each center. However, the presence of a basic comprehensive list may facilitate and ensure homogeneity and reproducibility of TID pretransplant consultations. Nevertheless, we acknowledge the significant paucity of data on which the proposed TID checklist was constructed. Most of our suggested tests and interventions were the result of clinical experience and relevance, rather than evidence-based. There is an urgent need for higher-quality evidence to guide future efforts, which would allow for a more efficient and cost-effective design of similar TID checklists in the future. Furthermore, the term and definition of "interventions" used in this study might have been arbitrary. However, we used clear-cut clinical objectives to try and quantify clinical interventions that would otherwise have not been possible to describe and assess in a tangible manner.

In conclusion, we describe a structured, clearly defined, and comprehensive pretransplant checklist for an efficient and accurate assessment of infectious disease risks and complications prior to an allogeneic HCT. Those data may allow providers to initiate a discussion on whether a TID consultation should be routinely performed prior to an allogeneic HCT and what should it ultimately include. Further studies or experiences like ours might help to define a global strategy or new models of care to be implemented in transplantation centers worldwide in the future.

Notes

Author contributions. D. N. and S. M.-L. conceived the idea of the study and the principal study design and participated in data analysis, interpretation, and manuscript writing and review. V. P. performed data collection,

analysis, and manuscript writing and review. All other authors participated in manuscript writing and review.

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Patient consent. All patients included in this study had signed an informed consent upon admission for their transplantation to allow the use of their clinical data for clinical research. The study was approved by the Ethics Committee of the University of Geneva (2020-00410).

Data availability. The datasets analyzed for this study are available from the corresponding author upon request.

Potential conflicts of interest. Y. C. has received consulting fees for advisory board membership from MSD, Novartis, Incyte, BMS, Pfizer, AbbVie, Roche, Jazz, Gilead, Amgen, AstraZeneca, and Servier, and travel support from MSD, Roche, Gilead, Amgen, Incyte, AbbVie, Janssen, AstraZeneca, Jazz, and Sanofi, all via institution. D. N. has received consulting fees from MSD, Pfizer, Takeda, and Gilead and research grants from MSD and Pfizer. All other authors report no potential conflicts.

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